M is a moiety that confers endonuclease resistance on said component and which contains at least one nucleic acid base with a 3'-methoxylphosphonate;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached and comprises a 2',3'-dideoxyribose nucleotide; [and]

x is an integer of about 2; and

y is an integer.

Kindly add new claim 52.

--52 (New) A modified nucleotide compound capable of forming RNase H-sensitive hybrids and having improved nuclease resistance comprising at least one non-terminal moiety that confers nuclease resistance on said compound and contains at least one modified or unmodified nucleic acid base and at least one non-terminal phosphodiester-linked unmodified 2'deoxynucleoside moiety. --

REMARKS

The claims are 1-52. Claims 1, 18, 19, 21, 37, 41, 42, 50 and 51 are amended and new claim 52 is added to more particularly and distinctly claim Applicants' invention. No claim has been canceled.

Independent claims 1, 21, 41, and 51 have been amended to recite that in the claimed modified nucleotide compound, method of inhibiting the function of an RNA, method of treating a human or animal, at least one component of the modified nucleotide compound is either MN_3M, $\underline{(N)_xM(N)_y}$, $\underline{(N)_xM(N)_yM}$, $\underline{B(N)_xM(N)_y}$ or $\underline{(N)_xM(N)_yB}$. Independent claims 42 and 50 have been amended to recite that the claimed compound contains at least two separate nuclease resistant components. New claim 52 has been added to claim a modified nucleotide compound capable of forming RNase H-sensitive hybrids and having improved nuclease resistance characterized in that the compound has at least one non-terminal moiety conferring nuclease resistance and at least one non-terminal unmodified 2'deoxynucleoside moiety. Disclosure of these characteristics appears throughout the specification, including in particular the Examples. Accordingly, no new matter has been added by the claim amendments.

Claims 18, 19, and 37 have been amended merely to conform to the claims from which they depend.

Claims 1, 2, 4, 8, 12-14, 19, and 42-50 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Miller (*Biochimie*, 1985). It is said that Miller discloses methyl phosphonate linked oligonucleotides used in antisense inhibition which are encompassed by the rejected claims. In particular, Miller is said to disclose at page 772, Figure 3, an oligomer having the

formula ^{32}pTpGpCpApCpCpApT, wherein the notation "p" denotes a normal phosphodiester-linkage.

Claims 1-4, 12-14 and 42-50 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Stein. It is said that Stein discloses phosphorothioate and phosphodiester linked oligonucleotides for antisense usage including S-capped oligomers and non-fully modified oligomers.

Claims 1-51 stand rejected under 35 U.S.C. § 103 (b) as being unpatentable over Walder in view of Miller (U.S. Patent No. 4,469,863) and Inoue. It is said that Walder discloses that the most important element in the efficacy of antisense oligomers is that they not only retain normal hybridization properties to form RNA-DNA duplexes but also should form substrates that are recognized and cleaved by RNase H. Miller is said to disclose antisense oligomers with all methylphosphonate linkages which are resistant to nucleases and can form stable duplexes with complimentary mRNA and to disclose a partially modified oligomer. Inoue is said to disclose nucleotides modified at the 2'-deoxyribose site.

These rejections are respectfully traversed.

Applicants' invention as presently claimed is directed to a modified nucleotide compound (claims 1-20, 51 and 52), method of inhibiting the function of an RNA (claims 21-39), method of identifying a nucleotide compound having nuclease resistance and capable of forming an RNase substrate (claim 40), treating a human or animal (claim 41), and a compound having nuclease resistant compounds (claims 42-50).

The claimed modified nucleotide compounds comprise at least one component selected from the group:

MN_3M, $(N)_xM(N)_y$, $(N)_xM(N)_yM$, $B(N)_xM(N)_y$, and $(N)_yM(N)_xB$.

Such modified nucleotide compounds are employed in the claimed methods of inhibiting the function of RNA and treating a human or animal. The claimed compound contains at least two separate nuclease resistant components each consisting of two or more contiguous phosphodiester-linked 2'-deoxynucleosides.

It is respectfully submitted that none of the cited references discloses or suggests the claimed compounds or methods.

Miller (*Biochimie*, 1985) discloses oligodeoxyribonucleoside methylphosphonates in which either all of the normal charged phosphodiester linkages are replaced with nonionic 3'-5'

methylphosphonate linkages or all except the terminal phosphonate linkage is modified. These modified oligomers are described as being resistant to nuclease hydrolysis and can form stable hydrogen-bonded complexes with complimentary nucleotide sequences such as mRNA.

However, Miller neither discloses nor suggests not fully modifying all the internal phosphodiester linkages or that, by not fully modifying, the resultant nucleotide compound is nuclease resistant and capable of forming RNase H-sensitive hybrids. Such is the invention of the Applicants.

Miller specifically teaches fully modifying the oligonucleotide internal phosphodiester linkages to protect it from nucleases. It is silent as to RNase H-sensitivity and provides no instruction or guidance as to how a nuclease resistant nucleotide might also form RNase-H sensitive hybrids. There is no suggestion or other motivation in Miller that anything but full modification should be implemented for its oligodeoxyribonucleoside methylphosphonate compounds.

Therefore, it is respectfully submitted that Miller (*Biochimie*, 1985) neither discloses, suggests or otherwise renders unpatentable Applicants' presently claimed invention.

Stein reports on the synthesis, melting temperature and nuclease susceptibility of a series of phosphorothioate oligodeoxynucleotides analogs, either all PS or end-capped with several PS groups at both 3' and 5' ends. Stein also reports on the RNase-H activity of duplexes of poly-rA with S-dT_{40} (all PS) and normal O-dT_{40}. There is no report on the RNase-H activity of duplexes with end-capped oligodeoxynucleotides.

Stein either fully modifies its oligodeoxynucleotides or end-caps them. There is no disclosure of partially modifying the internal oligodeoxynucleotides. Further, as Stein teaches that its modified oligodeoxynucleotides are nuclease resistant and have increased RNase-H sensitivity, Stein provides no motivation to use oligodeoxynucleotides only partially modified internally.

Thus, it is respectfully submitted that Stein neither teaches, suggests nor otherwise renders unpatentable Applicants' claimed invention.

Walder states that an important element for an effective antisense oligomer is that it be recognized and cleaved by RNase-H. However, Walder does not disclose or suggest any means of modifying a nucleotide compound to decrease degradation while retaining RNase H-sensitivity. It most certainly does not suggest that modifying some of the internal nucleotides, with sufficient spacing between modifications, might yield both nuclease resistance and RNase-H sensitivity.

Miller (U.S. Patent No. 4,469,863) does not cure the deficiency of Walder. Miller is directed to fully modified oligomers and provides no disclosure or suggestion to only partially modify its oligomers, let alone that such would be RNase-H sensitive. (The Examiner's reference to Figure 3 of the Miller patent seems to be a misstatement and that the Examiner is actually referring to Figure 3 of the Miller article. As discussed above, the Miller article does not cure the defects of Walder.)

Inoue also does not cure the defects of Walder or Miller. Inoue is concerned with a oligoribodeoxynucleotide probe comprised of a modified RNA sequence attached to a DNA sequence attached to another modified RNA sequence. The modifications to the RNA sequences is to resist RNase-H -- quite the opposite effect desired by Walder. Further, there is no suggestion or motivation provided by Inoue to modify its probe for use in antisense.

Accordingly, it is respectfully submitted that none of Walder, Miller or Inoue disclose or suggest Applicants' invention; that there is no suggestion or motivation to combine the disclosures of Walder, Miller and/or Inoue; and that, even if combined, the references do not disclose, suggest or otherwise render unpatentable Applicants' claimed invention.

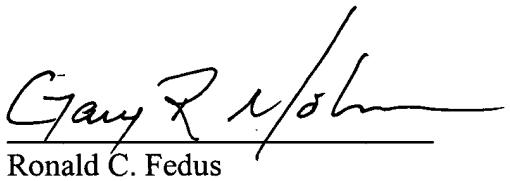
Wherefore, it is respectfully requested that the rejections be reconsidered and withdrawn, and the claims be allowed and passed to issuance.

If it would be helpful in furthering the prosecution of this application, the Examiner is respectfully requested to telephone Applicants' undersigned attorney at the number provided below.

A fee in the amount of $39.00 is deemed due in connection with the addition of independent claim 52 (small entity status having been previously established and still being applicable in this application). No other fee is deemed due in connection with the filing of this

Amendment. However, if any other fee(s) is due in connection with the filing of this Amendment, authorization is hereby given to charge the amount of such fee(s) to Deposit Account No. 05-1135.

Respectfully submitted,



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